Smart
DRUG SYSTEMS INC.
Smarter medicine through innovation.™

August 8, 2001

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20857

To Whom It May Concern:

We are filing this Suitability Petition to request permission to file an ANADA for a generic new animal drug which differs slightly from that of the pioneer product. We wish to file an ANADA to Merial Limited's IVOMEC® (ivermectin) 1% Injection for Cattle and Swine (NADA 128-409). Whereas the pioneer's product is a sterile solution for subcutaneous injection, our proposed generic product is a sterile compressed rod for subcutaneous injection containing a higher percentage of ivermectin.

1. **PETITIONER:** Smart Drug Systems, Inc.
7 Masons Island Road
Mystic, CT 06355

CITATION: Section 512 (n) (3) of the Federal Food, Drug and Cosmetic Act (the Act).

2. **ACTION REQUESTED:** We request permission to file an ANADA for a generic new animal drug which differs from that of the pioneer product by the following characteristics: Our generic product will be a sterile injectable compressed rod (NOT sustained release) containing between 35—60% ivermectin, whereas the pioneer product is a sterile injectable solution containing 1% ivermectin.

3. **STATEMENT OF GROUNDS:** There are 5 specific variances under the Act for which a Suitability Petition may be submitted. Our petition is for two of these allowed variances:

Allowable Variance #2, change of a dosage form. We are merely changing the dosage form from the pioneer's injectable sterile

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solution to our injectable sterile compressed rod.

Allowable Variance #3, change in strength of an ingredient. We are changing the strength of ivermectin in the formulation from 1% to between 35—60% (Additional studies will be conducted to determine the final percentage/concentration of ivermectin in the compressed rod. The final formulation will focus on one strength of ivermectin within this range.)

4. **ENVIRONMENTAL IMPACT:** We request a categorical exclusion under 21 CFR 25.30 (h) from the requirement to prepare an Environmental Assessment (EA), and have determined that no extraordinary circumstances exist [Federal Register 62 FR 40596; July 29, 1997]

5. **ECONOMIC IMPACT:** An Economic Impact statement will be provided upon request.

6. **CERTIFICATION:** A separate statement certifying that we have included all information unfavorable to this petition is included in this submission.

Additional essential elements of the petition:

1. **IDENTIFICATION OF DRUG:** The active ingredient in both the pioneer product and our generic is ivermectin.

2. **LABELING FOR THE PROPOSED PRODUCT:** Copies of the proposed labeling for the generic product and approved labeling for the pioneer product are included in this submission.

May we have your permission to file an ANADA for a generic new animal drug which differs from that of the pioneer product in that it is a sterile injectable compressed rod, containing a higher concentration of ivermectin, verses a sterile injectable solution?

Sincerely,

Jenaay M. Brown

Jenaay M. Brown DVM
Director, Regulatory Affairs

Attachment

I do hereby certify that I have included all information unfavorable to this petition; no unfavorable information has been intentionally withheld from this submission.

Jenaay M. Brown 8/8/01

Jenaay M. Brown DVM
Director, Regulatory Affairs

Date

PROPOSED GENERIC PRODUCT LABEL

SMART TAB™ (ivermectin) INJECTABLE COMPRESSED ROD FOR CATTLE AND SWINE

Active Ingredient(s): SMART TAB injectable rod is a sterile, ready to use compressed rod containing between 35—60% ivermectin, 10—25% sodium deoxycholate, 3% magnesium stearate and sucrose q.s. ad 100%. (Additional studies will be conducted to determine the final formulation. The final formulation will focus on one strength of ivermectin within this range.)

Indications: A parasiticide for the treatment and control of internal and external parasites in cattle and swine.

CATTLE: SMART TAB injectable rod is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, grubs, sucking lice and mange mites in cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae): *Ostertagia ostertagi* (including inhibited *O. ostertagi*), *O. lyrata, Haemonchus placei, Trichostrongylus axei, T. colubriformis, Cooperia* oncophora, *C. punctata, C. pectinata, Oesophagostomum radiatum, Bunostomum phlebotomum, Nematodirus helvatianus* (adults only), *N. spathiger* (adults only).

Lungworms (adults and fourth-stage larvae): *Dictyocaulus viviparus.*

Cattle grubs (parasitic stages): *Hypoderma bovis, H. lineatum*

Sucking Lice: *Linognathus vituki, Haematopinus eurystermus, Solenopotes capillatus.*

Mites (scabies): *Psoroptes ovis, (*syn. *P. communis* var. *bovis*), *Sarcoptes scabiei* var. *bovis.*

Persistent activity: SMART TAB injectable rod has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 28 days and *Ostertagia ostertagi* for 21 days after treatment; *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata,* and *Cooperia oncophora* for 14 days after treatment.

SWINE: SMART TAB injectable rod is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, lice, and mange mites in swine:
Gastrointestinal roundworms:

Large roundworm: *Ascaris suum* (adults and fourth-stage larvae).

Red stomach worm: *Hyostrongylus rubidus* (adults and fourth-stage larvae).

Nodular worm: *Oesophagostomum* spp. (adults and fourth-stage larvae)

Threadworm: *Strongyloides ransomi* (adults).

Somatic Roundworm Larvae:

Threadworm: *Strongyloides ransomi* (somatic larvae). Sows must be treated at least 7 days before farrowing to prevent infection in piglets.

Lungworms: *Metastrongylus* spp. (adults).

Lice: *Haematopinus suis.*

Mange mites: *Sarcoptes scabiei* var. *suis.*

REINDEER: For the treatment and control of warbles (*Oedemagena tarandi)* in reindeer (see Special Minor Use section under "Dosage and Administration").

AMERICAN BUFFALOES (BISON): For the treatment and control of grubs (*Hypoderma bovis)* in bison (see Special Minor Use section under "Dosage and Administration").

RANCH RAISED FOX: For treatment and control of ear mites (*Otodectes cynotis*).

Pharmacology: Product Description: Ivermectin is derived from the avermectins, a family of potent, broad-spectrum antiparasitic agents isolated from fermentation of *Streptomyces avermitilis.*

Mode of Action: Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which

occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The wide margin of safety is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Dosage and Administration:

Dosage:

CATTLE: SMART TAB injectable rod should be given only by subcutaneous injection under the loose skin in front of or behind the shoulder at the recommended dose level of 200 μg. ivermectin per kilogram of body weight.

SWINE: SMART TAB injectable rod should be given only by subcutaneous injection in the neck of swine at the recommended dose level of 300 μg. of ivermectin per kilogram of body weight.

Administration:

CATTLE: SMART TAB injectable rod is to be given subcutaneously only, to reduce the risk of potentially fatal clostridial infection of the injection site. Animals should be appropriately restrained to achieve the proper route of administration. Use the automatic syringe (gun) provided. Inject under the loose skin in front of or behind the shoulder.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infection. No special handling or protective clothing is necessary.

SWINE: SMART TAB injectable rod is to be given subcutaneously in the neck. Animals should be appropriately restrained to achieve the proper route of administration. Use the automatic syringe (gun) provided. Inject under the skin, immediately behind the ear.

As with any injection, sterile equipment should be used. The injection site should be cleaned and disinfected with alcohol before injection.

Recommended Treatment Program:

Swine: At the time of initiation any parasite control program, it is important to treat all breeding animals in the herd. After the initial treatment use SMART TAB injectable rod regularly as follows:

Breeding Animals:
Sows: Treat prior to farrowing, preferably 7-14 days before, to minimize infection of piglets.
Gilts: Treat 7-14 days prior to breeding. Treat 7-14 days prior to farrowing.
Boars: Frequently and need for treatments are dependent upon exposure. Treat at least two times a year
Feeder Pigs (Weaners/Growers/Finishers): All weaner/feeder pigs should be treated before placement in clean quarters.
Pigs exposed to contaminated soil or pasture may need retreatment if reinfection occurs.
Note:

1. SMART TAB injectable rod has a persistent drug level sufficient to control mite infestations throughout the egg to adult life cycle. However, since the ivermectin effect is not immediate, care must be taken to prevent reinfestation from exposure to untreated animals or contaminated facilities. Generally, pigs should bot be moved to clean quarters or exposed to uninfested pigs for approximately one week after treatment. Sows should be treated at least one week before farrowing to minimize transfer of mites to newborn baby pigs.
2. Louse eggs are unaffected by SMART TAB injectable rod and may require up to three weeks to hatch. Louse infestations developing from hatching eggs may require retreatment.
3. Consult a veterinarian for aid in the diagnosis and control of internal and external parasites of swine.

SPECIAL MINOR USE:

Reindeer: For the treatment and control of warbles (*Oedemagena tarandi)* in reindeer, administer at a rate of 200 µg. ivermectin per kilogram of bodyweight, subcutaneously. Follow use directions for cattle as described under Administration.

American Buffaloes (Bison): For the treatment and control of grubs (*Hypoderma bovis*) in bison, administer at a rate of 200 µg. ivermectin per

kilogram of bodyweight, subcutaneously. Follow use directions for cattle as described under Dosage and Administration.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

Contraindications: SMART TAB injectable rod for Cattle and Swine has been developed specifically for use in cattle, swine, reindeer and American bison only. The product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Precautions: Protect product from light.

Environmental Safety: Studies indicate that when ivermectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin may adversely affect fish and certain water-borne organisms on which they feed. Do not permit water runoff from feedlots or production sites to enter lakes, streams, or ponds. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

Caution: Transitory discomfort has been observed in some cattle following subcutaneous administration. A low incidence of soft tissue swelling at the injection site has been observed. These reactions have disappeared without treatment.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

Observe cattle for injection site reactions. Reactions may be due to clostridial infection and should be aggressively treated with appropriate antibiotics. If injection site infections are suspected, consult your veterinarian.

SMART TAB effectively controls all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season.

Destruction of *Hypoderma* larvae (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the possibility of fatalities. Killing *Hypoderma lineatum* when it is in the tissue surrounding the esophagus (gullet) may cause salivation and bloat, killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with SMART TAB, but can occur with any successful treatment of grubs. Cattle should be treated either before or after

these stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Cattle treated with SMART TAB after the end of heel fly season may be retreated with SMART TAB during the winter for internal parasites, mange mites, or sucking lice without danger of grub-related reactions. A planned parasite control program is recommended.

The product is not for intravenous or intramuscular use.

Warnings: Do not treat cattle within 35 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. Do not treat swine within 18 days of slaughter.

Do not treat reindeer within 8 weeks (56 days) of slaughter.

Do not treat bison within 8 weeks (56 days) of slaughter.

Keep this and all drugs out of the reach of children.

Presentation: [Packaging for SMART TAB will be described later—not yet developed.]

SMART TAB™ has been filed for by Smart Drug Systems, Inc., Mystic, CT USA.

PIONEER PRODUCT LABEL

IVOMEC 1% INJECTION FOR CATTLE AND SWINE

Active ingredients: IVOMEC® injection is a clear, ready-to-use, sterile solution containing 1% ivermectin, 40% glycerol formal and propylene glycol, q.s. ad 100%.

Indications: A parasiticide for the treatment and control of internal and external parasites in cattle and swine.

CATTLE: IVOMEC injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, grubs, sucking lice and mange mites in cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae): *Ostertagia ostertagi* (including inhibited *O. ostertagi*), *O. lyrata, Haemonchus placei, Trichostrongylus axei, T. colubriformis, Cooperia* oncophora, *C. punctata, C. pectinata, Oesophagostomum radiatum, Bunostomum phlebotomum, Nematodirus helvatianus* (adults only), *N. spathiger* (adults only).

Lungworms (adults and fourth-stage larvae): *Dictyocaulus viviparus.*

Cattle grubs (parasitic stages): *Hypoderma bovis, H. lineatum*

Sucking Lice: *Linognathus vituki, Haematopinus eurystermus, Solenopotes capillatus.*

Mites (scabies): *Psoroptes ovis, (*syn. *P. communis* var. *bovis*), *Sarcoptes scabiei* var. *bovis.*

Persistent activity: IVOMEC injection has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 28 days and *Ostertagia ostertagi* for 21 days after treatment; *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata,* and *Cooperia oncophora* for 14 days after treatment.

SWINE: IVOMEC injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, lice, and mange mites in swine:

Gastrointestinal roundworms:

Large roundworm: *Ascaris suum* (adults and fourth-stage larvae).

Red stomach worm: *Hyostrongylus rubidus* (adults and fourth-stage larvae).

Nodular worm: *Oesophagostomum* spp. (adults and fourth-stage larvae)

Threadworm: *Strongyloides ransomi* (adults).

Somatic Roundworm Larvae:

Threadworm: *Strongyloides ransomi* (somatic larvae). Sows must be treated at least 7 days before farrowing to prevent infection in piglets.

Lungworms: *Metastrongylus* spp. (adults).

Lice: *Haematopinus suis.*

Mange mites: *Sarcoptes scabiei* var. *suis.*

REINDEER: For the treatment and control of warbles (*Oedemagena tarandi)* in reindeer (see Special Minor Use section under "Dosage and Administration").

AMERICAN BUFFALOES (BISON): For the treatment and control of grubs (*Hypoderma bovis)* in bison (see Special Minor Use section under "Dosage and Administration").

RANCH RAISED FOX: For treatment and control of ear mites (*Otodectes cynotis*).

Pharmacology: Product Description: Ivermectin is derived from the avermectins, a family of potent, broad-spectrum antiparasitic agents isolated from fermentation of *Streptomyces avermitilis.*

Mode of Action: Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds

of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The wide margin of safety is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Dosage and Administration:

Dosage:

CATTLE: IVOMEC injection should be given only by subcutaneous injection under the loose skin in front of or behind the shoulder at the recommended dose level of 200 μg. ivermectin per kilogram of body weight. Each mL of IVOMEC contains 10 mg. ivermectin, sufficient to treat 110 lbs. (50 kg.) bodyweight. (Maximum 10 mL per injection site.)

SWINE: IVOMEC injection should be given only by subcutaneous injection in the neck of swine at the recommended dose level of 300 μg. of ivermectin per kilogram of body weight. Each mL of IVOMEC contains 10 mg. ivermectin sufficient to treat 75 lbs. bodyweight.

Administration:

CATTLE: IVOMEC injection is to be given subcutaneously only, to reduce the risk of potentially fatal clostridial infection of the injection site. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16 gauge ½ to ¾ inch needle is suggested. Inject under the loose skin in front of or behind the shoulder.

When using the 200, 500 or 1000 mL pack size, use only automatic syringe equipment.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infection. No special handling or protective clothing is necessary.

SWINE: IVOMEC injectable is to be given subcutaneously in the neck. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16 or 18 gauge needle is suggested for sows and boars, while an 18 or 20 gauge needle may be appropriate for young animals. Inject under the skin, immediately behind the ear.

When using the 200 mL, 500 mL or 1000 mL pack size, use only automatic syringe equipment.

As with any injection, sterile equipment should be used. The injection site should be cleaned and disinfected with alcohol before injection.

Recommended Treatment Program:

Swine: At the time of initiation any parasite control program, it is important to treat all breeding animals in the herd. After the initial treatment use IVOMEC (ivermectin) injection regularly as follows:

Breeding Animals:
Sows: Treat prior to farrowing, preferably 7-14 days before, to minimize infection of piglets.
Gilts: Treat 7-14 days prior to breeding. Treat 7-14 days prior to farrowing.
Boars: Frequently and need for treatments are dependent upon exposure. Treat at least two times a year
Feeder Pigs (Weaners/Growers/Finishers): All weaner/feeder pigs should be treated before placement in clean quarters.
Pigs exposed to contaminated soil or pasture may need retreatment if reinfection occurs.
Note:

1. IVOMEC injection has a persistent drug level sufficient to control mite infestations throughout the egg to adult life cycle. However, since the ivermectin effect is not immediate, care must be taken to prevent reinfestation from exposure to untreated animals or contaminated facilities. Generally, pigs should bot be moved to clean quarters or exposed to uninfested pigs for approximately one week after treatment. Sows should be treated at least one week before farrowing to minimize transfer of mites to newborn baby pigs.
2. Louse eggs are unaffected by IVOMEC injection and may require up to three weeks to hatch. Louse infestations developing from hatching eggs may require retreatment.
3. Consult a veterinarian for aid in the diagnosis and control of internal and external parasites of swine.

SPECIAL MINOR USE:

Reindeer: For the treatment and control of warbles (*Oedemagena tarandi)* in reindeer, administer at a rate of 200 μg. ivermectin per kilogram of

bodyweight, subcutaneously. Follow use directions for cattle as described under Administration.

American Buffaloes (Bison): For the treatment and control of grubs (*Hypoderma bovis*) in bison, administer at a rate of 200 μg. ivermectin per kilogram of bodyweight, subcutaneously. Follow use directions for cattle as described under Dosage and Administration.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

Contraindications: IVOMEC injection for Cattle and Swine has been developed specifically for use in cattle, swine, reindeer and American bison only. The product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Precautions: Protect product from light.

Environmental Safety: Studies indicate that when ivermectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin may adversely affect fish and certain water-borne organisms on which they feed. Do not permit water runoff from feedlots or production sites to enter lakes, streams, or ponds. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

Caution: Transitory discomfort has been observed in some cattle following subcutaneous administration. A low incidence of soft tissue swelling at the injection site has been observed. These reactions have disappeared without treatment. For cattle, divide doses greater than 10 mL between two injection sites to reduce occasional discomfort or site reaction.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

Observe cattle for injection site reactions. Reactions may be due to clostridial infection and should be aggressively treated with appropriate antibiotics. If injection site infections are suspected, consult your veterinarian.

IVOMEC injection effectively controls all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season.

Destruction of *Hypoderma* larvae (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the

possibility of fatalities. Killing *Hypoderma lineatum* when it is in the tissue surrounding the esophagus (gullet) may cause salivation and bloat, killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with IVOMEC, but can occur with any successful treatment of grubs. Cattle should be treated either before or after these stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Cattle treated with IVOMEC after the end of heel fly season may be retreated with IVOMEC during the winter for internal parasites, mange mites, or sucking lice without danger of grub-related reactions. A planned parasite control program is recommended.

The product is not for intravenous or intramuscular use.

Warnings: Do not treat cattle within 35 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. Do not treat swine within 18 days of slaughter.

Do not treat reindeer within 8 weeks (56 days) of slaughter.

Do not treat bison within 8 weeks (56 days) of slaughter.

Keep this and all drugs out of the reach of children.

Presentation: IVOMEC injection for Cattle and Swine is available in four ready-to-use pack sizes:

The 50 mL pack is a multiple dose, rubber-capped bottle. Each bottle contains sufficient solution to treat 10 head of 550 lb. (250 kg.) cattle or 100 head of 38 lb. (17.3 kg.) swine.

The 200 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 40 head of 550 lb. (250 kg.) cattle or 400 head of 38 lb. (17.3 kg.) swine.

The 500 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 100 head of 550 lb. (250 kg.) cattle or 1000 head of 38 lb. (17.3 kg.) swine

The 1000 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 200 head of 550 lb. (250 kg.) cattle or 2000 head of 38 lb. (17.3 kg.) swine. IVOMEC® is a registered trademark of Merial Limited, Iselin, NJ.